REMARKS

Claims 43, 44, 47, 49-72 and 74-77 are now pending in the application. Claim 76 has been amended to depend from claim 44, claim 73 has been canceled, and new claim 77 has been added in order to more particularly point out and distinctly claim that which the Applicant regards as the invention.

1. Obviousness-type Double Patenting Rejection

The Examiner has rejected claims 47, 65-71, 73, 74, and 76 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,290,551.

In response, Applicant will file a terminal disclaimer to overcome this rejection upon indication of allowable subject matter. However, Applicants respectfully point out that the subject matter of claim 47 is not obvious over the '551 patent, taken alone or in combination with the other references. Teachings in the antibody art have no relevance to protective immunotherapy.

2. Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 44, 47, 56-62, 65-72 and 75-76 under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification is enabling for a method of treating a malignant tumor in a human patient comprising administering the composition of claim 43 and BCG, but that the specification is not enabling for treatment of a malignant tumor in a human patient without administering BCG in combination with the claimed composition.

Applicant traverses this rejection. Numerous adjuvants are known, and the mere selection of one adjuvant, BCG, in the examples of the present invention should not serve to limit the invention thereby. Other adjuvants have been used effectively in tumor vaccines, such as McCune *et al.* (Cancer 43:1619, 1979; of record in this application), which describes the use of *C. parvum* as an adjuvant. Accordingly, Applicant submits that this rejection is in error and should be withdrawn.

3. Rejection Under 35 U.S.C. § 112, Fourth Paragraph

The Examiner has rejected claim 73 under 35 U.S.C. § 112, fourth paragraph because it does not further limit claim 47 from which it depends. Claim 73 has been canceled. The rejection with respect to this claim is now moot.

4. Rejection Under 35 U.S.C. § 102(a)

The Examiner has rejected claim 76 under 35 U.S.C. § 102(a) as being anticipated by Murphy et al. (Lab Investigation 62(1):70A, 1990). The Examiner states that Murphy et al. teach a method for treating melanoma comprising administering a therapeutically effective amount of autologous, irradiated DNP-conjugated melanoma cells. Claim 76 has been amended to depend from claim 44. Claim 44 is limited to a method for treating malignant tumors other than melanoma. Murphy et al. therefore does not anticipate amended claim 76 because Murphy et al. teaches treatment of melanoma. The grounds for the rejection of claim 76 under § 102(a) have thus been eliminated by the amendment of claim 76. Applicant respectfully requests that the rejection be withdrawn.

5. Rejection Under 35 U.S.C. § 102(b)

The Examiner has rejected claim 76 under 35 U.S.C. § 102(b) as being anticipated by Berd *et al.* (Proc. AACR 30:382, 1989). The Examiner states that Berd *et al.* teach a method for treating melanoma comprising administering a therapeutically effective amount of autologous, irradiated DNP-conjugated melanoma cells. Claim 76 has been amended to depend from claim 44. Claim 44 recites a method for treating malignant tumors other than melanoma. Berd *et al.* therefore does not anticipate amended claim 76 because Berd *et al.* teaches treatment of melanoma. The grounds for the rejection of claim 76 under § 102(b) have thus been eliminated by the amendment of claim 76. Applicant respectfully requests that the rejection be withdrawn.

6. Non-obviousness of the claimed invention

The Examiner has rejected the claims under 35 U.S.C. § 103 as allegedly being unpatentable over Berd *et al.* (Proc. AACR 30:382, 1989; hereinafter "Berd"), in view of U.S. Patent No. 5,702,704 (hereinafter "'704 patent"), U.S. Patent No. 5,626,843 (hereinafter "'843 patent), U. S. Patent No. 5,008,183 (hereinafter "'183 patent"), or U.S. Patent No. 4,232,001 (hereinafter "'001 patent") (hereinafter collectively "the Antibody Patents"); and Geczy *et al.* (J. Immunol. 19:189-203, 1970; hereinafter "Getzy"). The Examiner combines these references with additional (mostly cumulative) references to substantiate additional references. However, because this core set of references fails in all respects to anticipate the claimed invention, they are addressed prior to considering each of the obviousness rejections in turn.

a. The legal test for obviousness

A finding of obviousness under §103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. See Graham v. John Deere, 383 U.S. 1 (1966). A proper analysis of obviousness under §103 requires consideration of two factors: 1) whether the prior art suggests the claimed invention and 2) whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. See In re Vaeck, 947 F.2d 488, 493, 20 U.S.P.Q.2d (Fed. Cir. 1991)(citing In re Dow Chemical Co., 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988)). Both the suggestion and the reasonable expectation of success must exist in the prior art and not in the Applicant's disclosure. Id.

In order for a combination of prior art references to suggest a claimed invention, so as to render it obvious, an objective teaching must exist in the prior art that would lead a skilled artisan to combine its teachings. See In re Fritch, 972 F.2d 1260, 1266, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992)(citing In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988)). As the Federal Circuit has explained, "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so." See Fritch, 972 F.2d at 1266, 23 U.S.P.Q.2d at 1783. Furthermore, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to pieced [*sic*] together the teachings of the prior art so that the claimed invention is

rendered obvious. This court has previously stated that 'one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecated the claimed invention.'" Id.(quoting In re Gorman, 933 F.2d 982, 987, 18 U.S.P.Q.2d 1885 (Fed. Cir. 1991) and In re Fine, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988).

If the prior art does contain an objective teaching that provides an incentive or motivation to combine the art, this alone will not render a claimed invention obvious. The prior art must also provide a reasonable expectation of success for achieving the claimed invention in order to render the invention obvious. See In re O'Farrell, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

b. The core references do not suggest the claimed invention

i. Berd teaches melanoma vaccines

The Examiner states that Berd teaches a method of treating melanoma wherein a therapeutically effective amount of cyclophosphamide, 300 mg/M^2, is administered prior to autologous, irradiated DNP-conjugated melanoma cells and that

Berd teaches the treatment of melanoma patients with a vaccine comprised of autologous, irradiated melanoma cells conjugated to DNP and mixed with BCG preceded by low dose cyclophosphamide (300 mg/M^2). Berd teaches single injection of the vaccine and contains no objective teaching that would suggest to one of skill in the art to administer the vaccine six times at spaced intervals.

Berd does not teach or provide any reasonable expectation of success in achieving treatment for any tumor, and particularly for treating lung cancer, colon cancer, breast cancer,

kidney cancer, and prostate cancer. The other references cited by the Examiner do not supply the missing teaching, for the reasons set forth below.

The Examiner states (Office Action, page 11, lines 11-14) (emphasis added) that the "claimed method is anticipated because the method will inherently lead to an inflammatory immune response against the tumor, ..." when discussing the combination of Murphy (discussed *infra*, but which is cumulative to Berd) with the Antibody Patents (that teach conventional immunization to produce antibodies). Applicant respectfully points out that the inherency doctrine applies to a rejection for anticipation, as the Examiner correctly states but incorrectly applies in the context of an obviousness rejection.

ii. The various patents teach routine production of antisera

The Examiner states that the '704 patent, '843 patent, '183 patent, and '001 patent teach conventional immunization schedules wherein antigen is administered at least six times at spaced intervals. Indeed, the '183 patent teaches an assay for detecting the presence or absence of antibodies that bind to a human retrovirus antigen. The '001 patent teaches non-human antibodies to estrophilin. The '843 patent teaches the use of antibodies as immunosorbents for the treatment of AIDS. The '704 patent teaches antibodies that recognize advanced glycosylation endproducts and methods of using the antibodies for the measurement of the amount of advanced glycosylation end products in plants, animals, and cultivated and synthesized protein material. None of these patents contains an objective teaching of the use of antibodies for the treatment of human cancers. Even if these patents did teach antibody-based

(passive) immunotherapy, Applicant submits that such teaching would have no bearing on the present invention, which concerns active specific immunotherapy to tumors.

As the Examiner has noted, these patents teach conventional methods for generating an antigen specific antibody response. Such antibodies are useful as diagnostic reagents. The immunized subjects do not develop protective immunity to the immunogen; that is not the intention of the outcome. Thus, one might conclude that by following the teachings of these patents, one would be unlikely to generate a protective immune response. At the very least, there is no nexus between any of these references and the claimed invention.

Furthermore, these references do not teach or suggest at least six administrations of haptenized tumor cells (or any pathogenic antigen) to humans at spaced intervals for the treatment of cancer. No objective teaching thus exists in these patents that would suggest to or motivate one of skill in the art to administer antibodies to humans at least six times at spaced intervals in order to treat cancer. Such a conclusion demands hindsight gained from the instant application, but it is well settled that the references must contain the motivation for their combination with other references, and that hindsight is an improper basis for such a combination.

iii. Geczy only teaches contact DTH reagents

The Examiner states that Getzy teaches that halogenated dinitrobenzenes such as 1-chloro- and 1-fluoro-2,4-dinitrobenzene are commonly used to elicit delayed hypersensitivity. Applicant agrees. Indeed, there is not contention that contact reagents, which haptenize proteins, are well known in the art, and that a large number of such agents can be used as haptens in the practice of the present invention (*see, e.g.*, the specification at page 15, lines 6-9).

However, Geczy proposes that direct conjugation of DNFB with lymphocytes is necessary for transformation of the lymphocytes (Geczy, page 202, 4th full paragraph). In contrast, the present invention discloses that haptenization of tumor cells permits development of an effective anti-tumor response. Such a result appears to contradict Geczy's teachings, and thus is surprising and unexpected in view of this reference.

To the extent that Geczy describes dinitrobenzene reagents, it is merely cumulative to the Berd reference discussed above. It adds nothing to the teaching of that reference.

d. The rejection over Murphy, Berd, Geczy, and the Antibody Patents

The Examiner has rejected claims 47 and 65-76 as allegedly unpatentable over Murphy *et al.* (Lab Investigation 62(1):70A, 1990; hereinafter "Murphy") in view of the Antibody Patents, Berd, and Geczy.

The Examiner states that Murphy teaches a method for treating melanoma comprising sensitizing with DNCB, administering a therapeutically effective amount of cyclophosphamide, and administering a therapeutically effective amount of autologous, irradiated DNP-conjugated melanoma cells mixed with BCG. With respect to these teachings, Murphy is cumulative to Berd, which discloses each of these elements. The Examiner concedes that Murphy does not teach a method wherein a vaccine is boosted at least six times at spaced intervals, wherein cyclophosphamide is administered, wherein there is prior sensitization with 1-fluoro-2,4-nitrobenzene, or wherein at least one of the following is elicited upon administration to patients with an adjuvant: an inflammatory immune response against the tumor; a delayed-

type hypersensitivity response against the tumor; activation of T lymphocytes that infiltrate the tumor, or activation of T lymphocytes that infiltrate the tumor where the lymphocytes are predominately CD8+CD4-.

The Examiner concludes that it would have been *prima facie* obvious to combine the methods of Murphy and the cited patents because it is conventional to repeat antigen administration at least six times at spaced intervals. The Examiner further concludes that the claimed method is anticipated because the method would inherently lead to an inflammatory immune response against a tumor, a delayed-type hypersensitivity response against the tumor, activated T lymphocytes that infiltrate the tumor, and activated T lymphocytes that infiltrate the tumor in which the lymphocytes are predominately CD8+CD4-. The Examiner further concludes that it would have been *prima facie* obvious to use a dose of 300 mg/M^2 of cyclophosphamide in the method of Murphy because Berd teaches that dose is therapeutically effective in a method that uses the same haptenized melanoma cells with the same population of patients. The Examiner finally concludes that it would have been *prima facie* obvious to substitute DNFB for the DNCB of Murphy because Getzy teaches that dinitrobenzenes such as 1-chloro- and 1-fluoro-2,4-dinitrobenzenes are commonly used to elicit delayed hypersensitivity. The Examiner states that the burden is on the Applicant to prove that the method of the prior art does not result in prolonged survival of the patient and is functionally different than the method taught by the prior art.

In response, Applicant respectfully points out that for the reasons set forth above, the Examiner's rejection fails to establish *prima facie* obviousness. In short, Murphy and/or Berd fail to teach an effective vaccine composition or method of treatment for treating a non-

melanoma malignant tumor in a human patient. The Antibody Patents, which as the Examiner concedes merely teach conventional methods for generating antibodies for immunoassays or immune binding, provide no missing teaching. Similarly, Geczy fails to provide any teaching pertinent to the claimed compositions and methods. It merely reports well known observations about contact antigens, and proposes a mechanism by which they transform responding lymphocytes.

Accordingly, this rejection is in error and should be withdrawn.

e. The rejection over Berd, the Antibody Patents, and Geczy

The Examiner has rejected claims 47 and 65-76 as allegedly unpatentable over Berd, the Antibody Patents, and Geczy.

For the reasons discussed in detail above, this rejection is in error and should be withdrawn.

f. The rejection over Berd, the Antibody Patents, and Geczy in view of Wiseman

The Examiner has rejected claims 43, 44, 47, and 49-76 as unpatentable over Berd, the Antibody Patents, and Geczy, and further in view of Wiseman. The Examiner states that Wiseman teaches compositions comprising autologous irradiated melanoma cancer cells, lung cancer cells, colon cancer cells, and kidney cancer cells, which are administered to treat patients suffering from the respective cancers, and that the patients were pretreated with 300 mg/M^2 cyclophosphamide. This pre-treatment resulted in increased immunological response to

the cancer. Thus, the Examiner contends that it would have been *prima facie* obvious to substitute the cancers described in Wiseman for melanoma described in Berd.

Applicant respectfully disagrees. As discussed above, there is no reasonable expectation of successfully implementing the vaccination program described with respect to melanoma in Berd to other tumor types. This reference provides "preliminary" results that "may represent a significant advance in the immunotherapy of human melanoma." Thus, it lacks any reasonable expectation of an effective treatment for tumors in general, or even melanoma in particular.

Wiseman does not supply the missing teaching. Instead, Wiseman teaches an alternative form of immunotherapy that depends on the route of administration: intralymphatic immunization. This alternative, which Wiseman reports favorably, in no way suggests a deficiency or problem that would lead one of ordinary skill in the art to seek an alternative immunization strategy.

Thus, the references lack any objective teaching to combine their disclosures. Moreover, even if combined, the lack of any reasonable expectation of success from the disclosure of Berd precludes determining that the invention is obvious. Accordingly, the Examiner's rejection is overcome and should be withdrawn.

g. The rejection over Berd, the Antibody Patents, Geczy, and Berd 1983

The Examiner has rejected claims 43, 44, 47, and 49-76 as allegedly unpatentable over Berd, the Antibody Patents, Geczy, and Berd *et al* (Proc. Am. Soc. Clin. Oncol. 1983, 2:56; hereinafter "Berd 1983"). Berd, the Antibody Patents, and Geczy are discussed above. The

Examiner states that Berd 1983 teaches pre-administration of cyclophosphamide prior to administration of an autologous tumor cell/BCG vaccine, and that this pre-treatment resulted in delayed-type hypersensitivity.

Applicant submits that the teaching of Berd 1983 is cumulative to the teaching of Berd, which also discloses administration of cyclophosphamide three days prior to immunization with the autologous cell vaccine. Berd 1983 does not supply any of the other missing teaching. In particular, this reference fails to provide any teaching concerning a haptenized tumor cell vaccine or methods of treating cancer using such a vaccine.

In view of the foregoing remarks, Applicant submits that this rejection is in error and should be withdrawn.

h. The rejection over Berd, the Antibody Patents, Geczy, and Sanda and Moody

The Examiner has rejected claims 43, 44, 47, and 49-76 as allegedly unpatentable over Berd, the Antibody Patents, Geczy, further in view of Sanda *et al.* (J. Cellular Biochem. Suppl. 17(D):120; hereinafter "Sanda") and Moody *et al.* (J. Urol. 1991, 145:293A). Berd, the Antibody Patents, and Geczy are discussed above. The Examiner states that Moody teaches that lymphokine-transfected prostate cells generate an anti-tumor effect *in vivo*, and that Sanda addresses the feasibility of gene therapy for human prostate cancer. These references appear to be relevant because they suggest methods of anti-prostate cancer therapy.

The deficiencies of Berd, the Antibody Patents, and Geczy have been discussed above. Applicant respectfully submits that Sanda and Moody fail to supply the missing teaching of the primary group of references. Indeed, both Sanda and Moody propose an alternative cancer

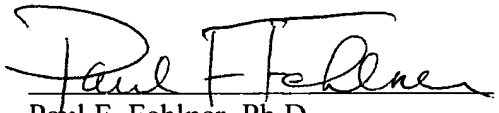
therapy, in which the tumor cells are modified to express immunostimulatory cytokines. This alternative form of treatment: gene therapy. While Sanda merely reports the ability to transfect tumor cells with a retrovirus vector, Moody reports that prostate cancer cells that secrete IL-2 provide protection from an otherwise lethal tumor, and give short-lived protection against subsequent challenge. Neither reference suggests that there is a deficiency, or provides any motivation to decorate the tumor cells with hapten in order to elicit an effective immune response. Thus, there is no objective reason to combine these references with the core group, much less any expectation of success in using haptenized tumor cells (instead of gene therapy) to elicit treatment for cancer.

For the foregoing reasons, the Examiner's rejection is overcome and should be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendment and remarks in the file history of the above-identified application. The claims as amended satisfy the requirements for patentability under 35 U.S.C. §§ 102, 103, and 112 and are, therefore, in condition for allowance. If any issue remains of concern, the Examiner is requested to contact the undersigned by telephone. Early allowance of the claims is earnestly solicited.

Respectfully submitted,



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